

case), the unexpected results must simply be shown to be attributed to the novel subject matter in order to overcome a *prima facie* case of obviousness.

In this case, superior results are directly attributable to the unique combination of elements claimed, e.g., the use of the $\alpha 1$ secretion signal from *S. cerevisiae* to induce secretory expression of an MK protein. Specifically, the applicants have shown that using the secretion signal unique to MK results in low yield and the predominance of sugar-bound MK (i.e., the expression of intact MK protein is low). Conversely, ligation of the MK protein cDNA immediately downstream of the prepro-sequence of $\alpha 1$ factor gene of *S. cerevisiae* under the regulation of the AOX1 promoter from *P. pastoris* results in a marked increase in expression of intact MK protein. See specification at p. 3, lines 12-16. For example, as discussed in Example 3, the expression level of MK produced using the $\alpha 1$ factor as the secretion signal (pPIC9K-4AhMK) was 100 times that detected using the PHO1 secretion signal (PHILS1-3AhMK) and 3 to 5 times that detected using the secretion signal unique to MK (PHILD4-hMK). Thus, the applicants' data demonstrates the advantageous and unexpected benefits of using the instantly claimed secretion signal.

Contrary to the current invention, Davis et al. suggest that the secretion signal may be selected either from the *S. cerevisiae* AMF (i.e., the $\alpha 1$ factor) or the native protein secretion signal (see Abstract, lines 3-4 as well as p. 7, lines 9-20; p. 11, lines 29-34; and p. 13, lines 3-29). Thus, the Davis reference fails to recognize or even suggest the criticality of using the claimed secretion signal sequence to achieve unexpected high levels of expression of the MK protein.

Thus, the unexpected results are commensurate with the scope of the claims and sufficient to rebut a *prima facie* case of obviousness. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-5, 8, and 10-12 under 35 U.S.C. §103.

Finally, with regard to the drawings in the subject application, the applicants are attaching for the Examiner's convenience evidence that the drawings were, in fact, submitted (and received by the Patent Office) at the time of filing. This evidence includes the Notice of Acceptance of Application under 35 U.S.C. §371, which acknowledges the receipt of the International Application (IA) and the English translation of the IA. It cannot be disputed that the IA contained the drawings. The applicants are further submitting a copy of the official Filing Receipt, which specifically acknowledges 17 drawings. The applicants appreciate that the drawings may have inadvertently

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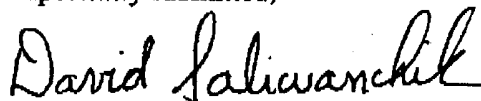
been separated from the file and, therefore, have provided new copies of the drawings. However, it would be an unfair and unnecessary burden for the applicants to be required to petition to the Patent Office to have these drawings entered when the record so clearly indicates that they were received by the Patent Office at the time of filing.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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